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Cigarette smoking and leukemia: results from the Lutheran Brotherhood Cohort Study

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In a 20-year follow-up (1966-86) of 17,633 White males who described tobacco use in a mailed questionnaire sent in 1966, there were 74 deaths from leukemia (including 30 myeloid, 30 lymphatic, and 14 other and unspecified leukemia). Among men who ever smoked cigarettes, increased risks were observed for lymphatic (relative risk [RR] = 2.7), and other and unspecified leukemia (RR = 1.5); risks rose with increasing number of cigarettes smoked, although the dose-response relationship was statistically significant only for total leukemia. Mortality from myeloid leukemia was not elevated, except among those smoking over a pack of cigarettes per day. Results from this cohort support a relationship between cigarette smoking and leukemia. Further studies are needed to elucidate subtype associations with cigarette smoking.

Key words: Cigarette smoking, leukemia, prospective study, United States.

Introduction

Although cigarette smoking was first reported as an important risk factor for lung cancer in 1950, a possible association with leukemia was suggested only recently in 1986.[1] Since then, a number of cohort[2-5] and case-control studies[6,7] have shown elevated occurrence of leukemia, particularly myeloid leukemia, among smokers, while other studies have observed no significant associations with smoking.[8-13] To assess further the association of cigarette smoking and leukemia, results are presented from a cohort study of 17,633 White men.

Methods

Eligible subjects were White male policy-holders of the Lutheran Brotherhood Insurance Society ($n = 26{,}030$). A mailed questionnaire sent in 1966 to members aged 35 and older was returned by 17,633 or 68.5 percent of the eligible subjects after three mailings, with respondents differing little from nonrespondents in age, urban/rural residence, policy status, and cancer mortality.[14] The questionnaire obtained information on tobacco use, diet, and demographic background. Most study subjects resided in the upper midwest and northeast regions of the United States. Compared with the US general population, a higher proportion of study subjects were farmers from rural areas and Norwegian or Scandinavian in heritage.[15]

After 20 years and 286,731 person-years of follow-up (1967-86), there were 4,513 deaths, including 1,033 cancer deaths. During the study period, 4,027 (23 percent) subjects were lost to follow-up primarily due to lapsed policies or discontinuation of policies after premium maturity. Death certificates were coded for

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Table 1. Relative risk (RR) of death from leukemia associated with tobacco use, Lutheran Brotherhood cohort, 1966-86

Tobacco use[a]	PY[b]	Myeloid leukemia		Lymphatic leukemia		Other and unspecified leukemia		Total leukemia	
		No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)
Never any tobacco use	58,888	8	1.0 —	5	1.0 —	2	1.0 —	15	1.0 —
Any tobacco use[d]	218,200	22	0.8 (0.3-1.7)	24	1.4 (0.5-3.5)	11	1.5 (0.3-6.8)	57	1.1 (0.6-1.9)
Cigarettes only	48,823	2	0.3 (0.1-1.6)	8	2.7 (0.9-8.3)	2	1.5 (0.2-10.3)	12	1.2 (0.6-2.6)
Pipes and/or cigars only	13,676	2	1.1 (0.2-5.0)	1	0.7 (0.1-6.1)	0	— —	3	0.8 (0.2-2.7)
Cigarettes and other tobacco use[e]	134,112	17	1.0 (0.4-2.2)	15	1.5 (0.6-4.2)	8	1.8 (0.4-8.6)	40	1.3 (0.7-2.3)

[a] Does not include smokeless-tobacco users and those with unknown tobacco use because of small numbers.
[b] PY = number of person-years.
[c] Adjusted for age; CI = 95% confidence interval.
[d] Tobacco-use categories refer to ever-users.
[e] Does not include cigarette smokers whose use of other tobacco is unknown.

underlying and contributory causes of death by the nosologist of the Minnesota State Department of Health. Leukemia deaths (International Classification of Diseases Eighth Revision, codes 204-207) were classified further as myeloid (comprised of both myeloid and monocytic subtypes, ICD8 codes 205 and 206), lymphatic (ICD8 Code 204), or other and unspecified (ICD8 Code 207).

A Poisson-regression program for modeling hazard functions was used to calculate age-adjusted relative risks (RR), with the hazard function assumed to be constant in each age interval.[16,17] Five-year age intervals were used, with RRs calculated for each age stratum and summarized over all strata for the selected variables. Person-years were accumulated up to death, loss to follow-up, or 1986. Likelihood ratio tests for trend were performed using subjects who never used tobacco as the reference group.

Results

In the 20-year follow-up, there were 74 deaths from leukemia, including 30 classified as myeloid, 30 as lymphatic, and 14 as other and unspecified (two with unknown smoking history not shown in Table 1). Risk of death from leukemia did not vary significantly by level of education, urban/rural status, occupation/industry, place of birth, or marital status (data not shown).

Risks of lymphatic, and other and unspecified, leukemia were increased 40 percent and 50 percent (neither statistically significant), respectively, among tobacco users (Table 1). Mortality from myeloid leukemia, however, was not increased and risk for total leukemia was elevated only slightly. Elevated risks for lymphatic, and other and unspecified, leukemia were found among men who smoked cigarettes only or cigarettes plus other forms of tobacco, but not among the small numbers of exclusively cigar or pipe smokers.

When cigarette smoking was examined by amount smoked per day, a statistically significant trend was found for total leukemia, and dose-response patterns (nonsignificant) were observed for lymphatic, and for other and unspecified, leukemia (Table 2). A slight excess (a 30 percent increase) was seen for myeloid leukemia among smokers of more than one pack per day. The risk of each type of leukemia was somewhat higher among ex-smokers than among current smokers, but the numbers of leukemia deaths were few in each group (data not shown).

Discussion

Excess mortality from lymphatic, and other and unspecified, leukemia was noted in relation to cigarette smoking in this cohort of White American men, with risks increasing by amount smoked. Except among heavy smokers, we did not observe any excess risk for myeloid leukemia.

In contrast to the present investigation, previous

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Table 2. Relative risk (RR) of death from leukemia associated with cigarette smoking, Lutheran Brotherhood cohort, 1966-86

Tobacco use[a]	PY[b]	Myeloid leukemia		Lymphatic leukemia		Other and unspecified leukemia		Total leukemia	
		No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)	No. deaths	RR[c] (CI)
Never any tobacco use	58,888	8	1.0 —	5	1.0 —	2	1.0 —	15	1.0 —
Ever smoked cigarettes[d]	190,637	19	0.8 (0.3-1.8)	23	1.7 (0.6-4.4)	10	1.7 (0.4-7.6)	52	1.2 (0.7-2.1)
≤ 10 cigs/day	63,575	5	0.5 (0.2-1.6)	9	1.5 (0.5-4.6)	1	0.4 (0.0-4.5)	15	0.9 (0.4-1.7)
11-20 cigs/day	80,230	8	0.8 (0.3-2.1)	9	1.7 (0.6-5.2)	6	2.5 (0.5-12.5)	23	1.3 (0.7-2.6)
> 20 cigs/day	43,268	6	1.3 (0.5-3.8)	4	1.9 (0.5-7.2)	3	3.0 (0.5-18.2)	13	1.8 (0.8-3.7)
P for trend			$P = 0.68$		$P = 0.11$		$P = 0.06$		$P = 0.04$

[a] Missing data not included.
[b] PY = number of person-years.
[c] Adjusted for age; CI = 95% confidence interval.
[d] Includes current and ex-smokers.

cohort studies of US veterans,[2,3] American Cancer Society volunteers,[4] Seventh Day Adventists,[5] and college graduates[18] generally reported statistically significant excesses for myeloid leukemia (RRs ranging from 1.5 to 2.5) among cigarette smokers, often with dose-response gradients. Cigarette smokers in two of these cohorts also were observed to have elevated risk of lymphatic leukemia.[2,4] Combined with these reports, our data suggest that the association between smoking and leukemia may affect essentially all subtypes. Although the majority of investigations support a link between cigarette smoking and leukemia, two cohort[8,9] and several case-control studies[10-13] have shown no relationship with cigarette smoking.

Specific substances in cigarette tobacco smoke, including benzene, various acids, and agricultural chemicals, have been associated with lymphatic leukemia.[19] Occupational studies have linked lymphatic leukemia to benzene and other solvents,[20-23] as well as to acid-containing chemicals, aliphatic and chlorinated hydrocarbons, and pesticides.[24-27] Thus, it is biologically plausible that not only myeloid but also lymphatic leukemia may be linked with exposure to some of the carcinogenic and mutagenic constituents of cigarette smoke.

On the other hand, the absence of a significant excess and clear dose-response gradient for myeloid leukemia among cigarette smokers in the Lutheran Brotherhood cohort may have resulted from misclassification of leukemia subtypes, a common problem in leukemia mortality studies.[28] Deaths actually due to myeloid leukemia may have been specified incompletely on death certificates as acute leukemia or leukemia without additional subtype characterization or, less likely, incorrectly designated as lymphatic leukemia. Therefore, risk estimates for total leukemia mortality may be more valid than subtype estimates.

Two studies have reported an excess of leukemia among coffee drinkers, although the findings were not adjusted for cigarette smoking.[29,30] We did not find a significant overall association between coffee drinking and leukemia in our data. However, we did detect a smoking-coffee interaction, with an enhanced effect of smoking on leukemia among men who were heavy coffee drinkers. The apparent effect-modification by coffee drinking of the smoking-leukemia relationship may be a chance finding, but it also could be signaling that the metabolism of cigarette smoke constituents into leukemogens is enhanced in the presence of caffeine (or other coffee components).

In addition to the small number of leukemia deaths, this study has other limitations. Twenty-three percent of the members ($n = 4,027$) were lost to follow-up by the end of the 20-year study period due to lapsed policies or discontinuation of policies after premium maturity. We examined the exposures of these individuals, including smoking and dietary habits, and found no significant differences between them and the remainder of the cohort.[31] Moreover, a special investigation of lost-to-follow-up subjects was initiated at 11.5 years of follow-up that found little difference in mortality with those whose vital status was known.[14]

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Because smoking history was obtained once in 1966, the category of 'current smokers' includes subjects who may have quit later in the study. Hence, the RRs for cigarette smoking may be underestimates, since large numbers of middle-aged American men stopped smoking during the period of the late 1960s through the 1980s.[32] We examined the risk of leukemia among smokers for the first and second decades of follow-up and found no significant differences, although risks in the second decade of follow-up tended to be higher than those in the first decade.

It is also possible that cohort members, defined as insurance policy holders, may have under-reported cigarette smoking on the study questionnaire because of insurance eligibility concerns, although confidentiality was assured in the 1966 cover letter to respondents. Also, respondents may have underestimated their smoking because of awareness of the scientific reports linking cigarette smoking with increased mortality. Finally, the Lutheran Brotherhood cohort included more farmers, rural residents, and persons of Scandinavian heritage than in the US as a whole.[15] Although farmers have been reported to smoke less than the general population and have been found to have higher leukemia risk in some studies,[27] farmers in the Lutheran Brotherhood cohort did not have a higher leukemia risk than non-farmers, nor was there a significant interaction of cigarette smoking with the occupation of farmer.

In conclusion, our findings provide support for an association of cigarette smoking with leukemia. Future research efforts should attempt to specify the relationship between cigarette smoking and morphologically verified leukemia subtypes, with emphasis on both lymphatic and myeloid subtypes.

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